



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: A61L 31/10		A1	(11) International Publication Number: WO 00/02599
			(43) International Publication Date: 20 January 2000 (20.01.2000)
(21) International Application Number: PCT/IL99/00376		Published	
(22) International Filing Date: 08 July 1999 (08.07.1999)			
(30) Priority Data: 09/112,125 08 July 1998 (08.07.1998) US			
(60) Parent Application or Grant ADVANCED BIOPATENTABLE COATINGS INC. [/]; O. BINDERMAN, Itzhak [/]; O. BINDERMAN, Itzhak [/]; O. WOLFF, BREGMAN AND GOLLER ; O.			

(54) Title: **BIOCOMPATIBLE METALLIC STENTS WITH HYDROXY METHACRYLATE COATING**
 (54) Titre: **STENT METALLIQUE BIOPATENTABLE A REVETEMENT D'HYDROXYMETHACRYLATE**

(57) Abstract

The invention provides a hemo-compatible, restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivate selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethoxyethyl methacrylate) PMEEMA, poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof.

(57) Abrégé

L'invention concerne un stent métallique hémocompatible, inhibant la resténose, comprenant un revêtement de polyhydroxyméthacrylate sélectionné dans le groupe comprenant le polyhydroxyéthyl méthacrylate (PHEMA), le poly(hydroxyéthoxyéthyl méthacrylate) (PHEEMA), le poly(hydroxydiéthoxyéthyl méthacrylate) (PHDEEMA), le poly(méthoxyéthyl méthacrylate) (PMEMA), le poly(méthoxyéthoxyéthyl méthacrylate) (PMEEMA), le poly(méthoxydiéthoxyéthyl méthacrylate) (PMDEEMA), le poly(éthyléneglycol diméthacrylate) (PEGDMA), ainsi que des mélanges de ces composés.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61L 31/10		(11) International Publication Number: WO 00/02599
		(43) International Publication Date: 20 January 2000 (20.01.00)
<p>(21) International Application Number: PCT/IL99/00376</p> <p>(22) International Filing Date: 8 July 1999 (08.07.99)</p> <p>(30) Priority Data: 09/112,125 8 July 1998 (08.07.98) US</p> <p>(71) Applicant (<i>for all designated States except US</i>): ADVANCED BIOCOMPATIBLE COATINGS INC. [US/US]; 1313 N. Market Street, Wilmington, DE 19801-1151 (US).</p> <p>(72) Inventor; and</p> <p>(73) Inventor/Applicant (<i>for US only</i>): BINDERMAN, Itzhak [IL/IL]; Fivel Street 13, 62995 Tel-Aviv (IL).</p> <p>(74) Agent: WOLFF, BREGMAN AND GOLIER; P.O. Box 1352, 91013 Jerusalem (IL).</p>		
<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SI, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>		
<p>(54) Title: BIOCOMPATIBLE METALLIC STENTS WITH HYDROXY METHACRYLATE COATING</p> <p>(57) Abstract</p> <p>The invention provides a hemo-compatible, restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivatve selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethoxyethyl methacrylate) PMEEMA, poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	RS	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	MN	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MR	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MW	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MX	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	NE	Mexico	US	United States of America
CA	Canada	IT	Italy	NL	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NO	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NZ	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	PL	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PT	Poland		
CM	Cameroon	KR	Republic of Korea	RO	Portugal		
CN	China	KZ	Kazakhstan	RU	Romania		
CU	Cuba	LC	Saint Lucia	SD	Russian Federation		
CZ	Czech Republic	LI	Lithuania	SE	Sudan		
DE	Germany	LK	Sri Lanka	SG	Sweden		
DK	Denmark	LR	Liberia		Singapore		
EE	Estonia						

Description

5

10

15

20

25

30

35

40

45

50

55

5

BIOCOMPATIBLE METALLIC STENTS WITH HYDROXY METHACRYLATE COATING

10

Technical Field

15

The present invention relates to the application of a coating of a poly-hydroxymethacrylate derivative to improve the biocompatibility of metal stents intended for implantation or insertion. More specifically, the present invention relates to the coating of metallic stents with effective amounts of a coating of a poly-hydroxymethacrylate derivative which will drastically increase the thromboresistance of the stent, as well as prevent any significant deposit of protein, or the occurrence of mineral encrustation, and thereby achieve inhibition of restenosis.

20

25

Background Art

30

35

Advances in medical and surgical technology involving the introduction of implantation of foreign materials, such as stents, catheters, prostheses, etc. into body-tissue make the search for the development of materials that exhibit a long-term biocompatibility more pressing than ever before. A wide range of materials and polymers have been tested and used in medical device applications. These include polyethylene, polypropylene, polyvinylchloride, polyesters, polystyrene, polyurethane, silicone, polysulphone, polyamide, polytetrafluoroethylene, cellulose and its derivatives. Although they have excellent mechanical and physical properties, they were originally developed for the use in industrial manufacturing and not specifically for the biomedical field.

40

45

Foremost among the difficulties that need to be addressed within a medical or surgical context are the problems concerning the development of thromboresistant materials and coatings that will resist protein deposits and adverse vessel-wall reactions. Indeed, it is by now well-documented that adverse reactions between foreign or prosthetic surface and blood components, e.g. platelet-activation and thrombogenesis, constitute the single most important factor limiting the use of certain biomaterials. To prevent uncontrolled hemostasis, patients need to be

50

55

5

2

10

15

20

treated prophylactically with anti-coagulants, such as heparin or warfarin. In a considerable fraction of these cases, depending on the site of deployment of the implant, the patient needs to continue this medication indefinitely, necessitating a strictly controlled regime of drug-taking which effectively balances the patient on a narrow operational strip flanked by the dual dangers of uncontrolled bleeding on the one hand and the development of an embolism on the other, both obviously equally disastrous outcomes. Even if this treatment can be discontinued after a limited period of time, it complicates the procedure and significantly increases the patient's risk of post-operative bleeding and infection.

25

30

As a matter of fact, some biomedical applications are totally precluded by the thrombogenic potential of stents and/or synthetic polymers. An example of this is the small diameter vascular graft for use in coronary artery bypass. At present, all synthetic materials fail in this application and a patient requiring coronary bypass must first undergo a procedure to remove the saphenous vein from the leg. This vein is subsequently used to carry out the bypass itself. A biocompatible material would have an enormous benefit in this application.

35

40

With regard to the problem of protein deposition, this manifests itself whenever biological fluids come into contact with synthetic surfaces such as glass, steel or polymers. These deposits have an important impact on the course of subsequent events occurring at the surface such as platelet adhesion-activation for blood containing devices, or mineral encrustation on urological stents. The risk of thrombus formation is, in the case of some devices, also accompanied by the additional risk of infection as a result of the adhesion and proliferation of bacteria at the surface of a biomaterial.

45

50

Numerous experiments have been conducted aiming at improving the biocompatibility of stents and surgical implant-devices. Based on the experimental data, one of the most recent suggestions is to use an amphiphilic polyurethane coating on stents (see e.g., De Scheerder et al.: Biocompatibility of biodegradable and non-biodegradable polymer coated stents in porcine peripheral arteries. *Cardiovasc. Intervent. Radiol.* 18:4, Jul-Aug. 1995, pp.227-32).

55

5

3

Another approach is based on a discovery made by Chapman in the late 1970's [See e.g., Chapman, D., et al.: Biomembranes as models for polymer surfaces. *Biomaterials*. Vol. 7, July 1986, pp. 121-5, 126-31 and 252-8; Durrani, AA, Hayward, JA and Chapman, D : Biomembranes as models for polymer surfaces II; The syntheses of reactive species for covalent coupling of phosphorylcholine to polymer surfaces. *Biomaterials*, 7:2, 1986 Mar, pp. 121-5; Hall, B., et al.: Biomembranes as models for polymer surfaces. *Biomaterials*. Vol. 10, May 1989, p.219-224; and Hayward, JA, et al.: Biomembranes as models for polymer surfaces IV; ESCA analyses of a phosphorylcholine surface covalently bound to hydroxylated substrates. *Biomaterial*, 7:4, 1986 Jul. pp. 252-8], who observed that intact biological membranes are highly successful in preventing inappropriate blood clotting reactions. He went on to show that the phosphorylcholine head group is essential in imparting biocompatibility to the phospholipids in the cell-membrane. Some of the most promising and successful attempts of designing biocompatible coatings to date, try to harness these properties: by covalently binding a phosphorylcholine-group to a metal or polymer they attempt to mimic the external surface of biomembranes.

35 **Disclosure of the Invention**

The present invention is based on a different approach. Instead of coating the stent with polyurethane or any of the other polymers cited above, according to the present invention, a coating of a poly-hydroxy methacrylate derivative is applied to a metallic stent which results in a highly biocompatible and thromboresistant coating for said stents.

40 More particularly, according to the present invention there is now provided a hemo-compatible, restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivative.

45 The term poly-hydroxy methacrylate derivative, as used herein, is intended to include hydroxy, alkoxy, and dihydroxy, i.e. glycol derivatives.

50

55

5

4

More specifically, the present invention provides a hemo-compatible, 10 restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivative selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly 15 (methoxyethyl methacrylate) (PMEMA), poly (methoxyethoxyethyl methacrylate) PMEEMA, poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof.

20 In another aspect of the present invention there is now provided a process for producing hemo-compatible, restenosis inhibiting metallic stents including the steps of:

- 25 (a) coating a metallic stent with a liquid which contains a hydroxymethacrylate derivative selected from the group consisting of 2-hydroxyethyl-methacrylate; hydroxyethoxyethyl methacrylate, hydroxydiethoxyethyl methacrylate, methoxyethyl methacrylate, methoxyethoxyethyl methacrylate, methoxydiethoxyethyl methacrylate, ethylene glycol dimethacrylate and mixtures thereof;
- 30 (b) polymerization of said 2-hydroxy-methacrylate derivative into a polyhydroxymethacrylate derivative selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethoxyethyl methacrylate) 35 PMEEMA, poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof;
- 40 (c) cleaning the stent after polymerization to extract any remaining residues; and
- 45 (d) drying the same.

50

55

5

5

10 The present invention also provides a process for producing
hemo-compatible bioactive restenosis inhibiting metallic stents, comprising the
steps of:

15 a) coating a metallic stent with a liquid which contains
poly-hydroxyethylmethacrylate in liquid form;
b) cleaning the stent to extract any remaining residues; and
c) drying the same.

20 **Summary of the invention**

Unlike the approach pioneered by Chapman (*Ibid*), the present invention does
not aim at mimicking the cell-membrane directly. Rather, the aimed-for
25 biocompatibility is achieved by applying a coating of a poly-hydroxymethacrylate to
the metallic surface of a stent. Current uses of 2-hydroxyethyl-methacrylate
(hereinafter referred to as HEMA) or its polymer (hereinafter referred to as PHEMA)
30 include adhesives, artificial nails, lacquers, cosmetic compositions, UV-inks and
soft lens applications. Surfaces of plastic devices are modified with PHEMA.
Furthermore, it is also used as an anti-adhesive to prevent cell attachment in cell
cultures, and as an inducer of trabecular bone in dental implants. As such, its
35 non-toxicity and usefulness in medical and biological applications is
well-documented.

40 According to the present invention poly-HEMA is used as a biocompatigenic
coating for metal stents. This PHEMA coating renders the stents biocompatible by
covering the metallic surface with a uniformly distributed layer of strongly polar and
hence hydrophilic groups. As stated hereinbefore, in addition to PHEMA, there are
45 other acrylic-type polymers which are poly-hydroxymethacrylate derivatives and
which are similar in general structure to PHEMA:

50 Among these derivatives are poly (hydroxyethoxyethyl methacrylate)
(PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly
(methoxyethyl methacrylate) (PMEMA), poly (methoxyethoxyethyl methacrylate)
PMEEEMA, poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), and poly

5

6

10 (ethylene glycol dimethacrylate) (PEGDMA). The use of all these polymers and combinations thereof as coating on metallic stents is part of the present invention, although the invention will now be more specifically described with reference to the preferred PHEMA coating, it being understood that the description with regard to PHEMA is also applicable to said other polymeric coatings.

15

In a first preferred embodiment of the present invention the polymerization of the HEMA takes place directly on the metallic surface of the stent.

20

In a second preferred embodiment of the present invention the HEMA is polymerized partly before it comes to the surface of the stent.

25

In U.S. Patent 5,679,400 there is described a method for providing a therapeutic substance into a body lumen which involves providing a stent and applying to the stent a solution which includes a solvent, a polymer dissolved in the solvent and a therapeutic substance dispersed in the solvent. The polymers described in said patent include bioabsorbable polymers such as poly(lactic acid), poly(lactide-co-glycolide) and poly(hydroxybutyrate-co-valerate) and biostable polymers such as polyurethanes, silicones, polyesters, vinyl homopolymers and copolymers, acrylate homopolymers and copolymers, polyethers and cellulosics, however said patent does not teach or suggest the specific use of a coating of a polyhydroxymethacrylate derivative to a stent in the substantial absence of a therapeutic component in order to provide restenosis-inhibiting properties to said stent and the only acrylate polymer mentioned in said patent is an ethylene-methyl methacrylate copolymer, listed as one among tens of other named polymers.

30

35

40 Several explanations may be offered for the biocompatigenic nature of PHEMA. One possibility is that the strongly hydrophilic nature of the outside layer of PHEMA attracts a dense water-coat, thus preventing blood-corpuscles to come into direct contact with the stent, an event that normally triggers the thrombogenic reaction (see, e.g., Binderman, I., et al., Grafts of HTR Polymer versus Kiel Bone in Experimental Long Bone Defects in Rats, ASTM, PA 19103).

45

50

55

5

7

Alternatively, it may be the case that polar PHEMA coating attracts the polar
10 moiety on circulating phospholipids which then precipitate under the form of a lipid
bilayer. In this instance, biocompatibility would again be a consequence of
15 mimicking the thromboresistance of cell-membranes. If this latter hypothesis turns
out to be correct, it underscores the possibility of self-assembly and hence
self-repair of the very factor that induces biocompatibility. This is an extremely
20 desirable property for a stent, especially in locations where there are considerable
shear forces due to strong blood-circulation, such as heart and main arteries. In
addition, PHEMA coated stents prevent adverse cell reaction of the injured site, cell
growth, and restenosis.

Whatever the explanation, it has now been found that coating of the metallic
25 surface of stents with PHEMA results in the creation of a stable and highly
biocompatible coating which makes the stent thromboresistant and prevents the
deposition of protein and adverse vessel-wall reactions, thus vastly increasing their
value in surgical procedures.

30 Thus, the present invention enables the prevention or minimization of restenosis
that is evident in some cases with the introduction of metallic stents, by providing
hemo-compatible bioactive restenosis-inhibiting metallic stents.

35 2-Hydroxyethyl methacrylate (HEMA) can be polymerized into poly-HEMA
(PHEMA), which is a polymer exhibiting a strongly polar character. PHEMA shows
minimal bacterial or cell binding but excellent cell biocompatibility, no protein
40 deposition and no blood clotting. This means that blood plaques which might
trigger the development of a potentially fatal thrombus will not be formed. As there
is little or no bacterial adhesion, the risk of infections is minimized. PHEMA is a
coating which can be used on metal based stents, and which makes these stents
45 biocompatible. The stents can be made of stainless steel, Ti-based alloys, shape
memory alloys or any other metal, eventually in combination with synthetic or
biological materials. The stents are coated with the hydrophilic HEMA-monomer,
which is then polymerized by using dielectric heating, UV light, electron-beam
50

5

8

radiation, gamma-radiation, ozone initiation, X-rays, lasers, visible light, thermal 10 cure or any other means. Thus, said polymerization can be initiated by at least one of photopolymerization, ionic-polymerization, and chemical-polymerization.

15 After the polymerization procedure, the stent is placed in hot or boiling liquid, e.g. water to remove the remaining monomers. Such stents find applications in e.g. 20 vascular, endo-esophageal and urological stents, as well as for coronary artery bypass surgery or the repair of aneurysms, etc. .

In general, the procedure for preparing coated stents according to the present 25 invention is as follows:

A stock solution is prepared by dissolving the 2-hydroxyethyl methacrylate (HEMA), formula $C_6H_{10}O_3$, CAS Number 868-77-9, in ethanol. Other possible 30 solvents are dimethyl sulfoxide (DMSO), propanol, glycerol, ethylene glycol, cyclohexanol, toluene and dimethyl formamide (DMF). It is preferable to use the HEMA in an as pure as possible form, typically better than 98.4%. Typical 35 solutions are made by dissolving 120 mg HEMA in 1 ml 95% ethanol. The dissolving process is helped by shaking the solution and a storage at e.g. 37°C for 12 hrs. A separation of undissolved material can be reached by centrifuging at e.g. 40 2500 rpm for 30 min. Further dilution with ethanol can be used to produce coatings of various thickness. Polymerization is lightly inhibited by trace amounts of an inhibitor such as the methyl ether of hydroquinone (MEHQ). MEHQ should be present in a concentration within the range of 150 to 300 ppm, preferably 200 ppm. The HEMA can be modified by the addition of a cross linking agent such as 45 triethyleneglycol dimethacrylate, which comprises between about 0.1 and 6% of the HEMA, preferably 5%. Alternatively, tetraethyleneglycol dimethacrylate, diethyleneglycol dimethacrylate and monoethyleneglycol dimethacrylate can be used. A combination of these diesters can also be used.

50 After wetting the stents with the described solution, they can be air dried in a e.g. sterile environment (sterile lamina flow hood), or when inhibitors are applied, the polymerization can take place by means of a dielectric furnace, UV light or

55

5

9

controlled temperature chamber. The heating provides sufficient free radical activity to overcome the effect of the inhibitor, resulting in polymerization of the coating. The heating step is, e.g. about 1.5 minutes in duration in a dielectric furnace when the upper electrode is positioned about 5 mm above the stent. In order to remove any remaining HEMA monomer and/or traces of the inhibitor after the polymerization step, the stent is boiled in water for about 2 to 3 minutes after cooling down. This procedure will leach out any remaining HEMA monomer and/or inhibitor. After boiling, the stents can be dried at a slightly higher temperature. 2-hydroxyethyl methacrylate can be applied directly to the stent or with the help of a primer such as silanes.

In order to further improve the biocompatibility, the surface modification by selective alkaline hydrolysis was studied. It was found that the thickness of the modified layer can be influenced by the reaction temperature, NaOH concentrations and reaction time.

Using at least 30% NaOH, short reaction times and temperatures of at least 90°C, coatings with carboxylic groups in the surface layer were prepared. This method can be used for obtaining hydrophilic medical coatings with further improved properties and further increased biocompatibility.

The scope of the invention includes the coating with a poly-hydroxymethacrylate derivative of all metallic surfaces of stents of all types, as well for only metallic stents and for the coating of stents formed from the combination of metal with synthetic or biologic tissues.

40 Description of Preferred Embodiments

While the invention will now be described in connection with certain preferred embodiments in the following examples so that aspects thereof may be more fully understood and appreciated, it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the

5

10

particulars shown are by way of example and for purposes of illustrative discussion of
10 preferred embodiments of the present invention only and are presented in the cause of
providing what is believed to be the most useful and readily understood description of
formulation procedures as well as of the principles and conceptual aspects of the
invention.

15

Example 1

1. A stock solution is prepared by dissolving 120 mg 2-hydroxyethyl
methacrylate (HEMA), formula $C_6H_{10}O_3$, CAS Number 868-77-9, in 1 ml 95%
20 ethanol. It is preferable to use the HEMA in an as pure as possible form, typically
better than 98.4%.
2. The dissolving process is helped by shaking the solution for 1 hr. and storing
at 37 °C for 12 hr.
- 25 3. A separation of undissolved material is then reached by centrifuging at 2,500
rpm for 30 min.
4. Polymerization is lightly inhibited by utilizing trace amounts of an inhibitor (2
30 drops) and the methylether of hydroquinone (MEHQ) is utilized for this purpose.
5. The Palmaz-Schatz stent and a Wiktor stent were used in this particular
example. Other stents have been used in other tests.
- 35 6. The stents were thoroughly cleaned using laboratory detergents, and
washed in warm water.
7. The stents were left to air dry in a sterile environment (sterile lamina flow
hood).
- 40 8. The stents were then wetted with the solution by dipping them in the solution
to the point where their entire surface was submerged in the liquid.
9. Using a specially designed lever, the stents were lifted out of the solution at
45 a rate of 1 mm/sec. This facilitated the uniformity of the coat.
10. The stents were left to air dry in a sterile environment (sterile lamina flow
hood).
- 50 11. Steps 8-10 were repeated 4 times in order to get the appropriate coating
thickness.

5

11

10 12. The stents were moved to a UV light chamber and radiated for an additional 10 min. The stents were then placed in the chamber in a way that all sides of the stent were no more than 3 cm away from each lamp.

15 13. In order to remove any remaining HEMA monomer and/or traces of the inhibitor after the polymerization step, the stent was boiled in water for about 2 to 3 minutes after cooling down.

20 14. After boiling, the stents were dried at a slightly higher temperature. 15. The stents were then placed on an angioplasty balloon and were inflated to 85% of their range.

25 16. The stents were weighed and examined under a scanning microscope to determine the uniformity of the coat and its attachment to the stent surface.

17. The stents' surface appeared to be completely covered and to a sufficient 25 level of uniformity. Coating adhesion remained intact even under severe stress.

Example 2

30 1. A stock solution was prepared by dissolving 120 mg poly-hydroxyethyl methacrylate (PHEMA) IN 1 ML 95% ethanol. It is preferable to use the PHEMA in an as pure as possible form, typically better than 98.4%.

35 2. The dissolving process was helped by heating the solution to 75 °C and shaking the solution for 1 hr.

3. A separation of undissolved material was reached by centrifuging at 3.g. 2500 rpm for 30 min.

40 4. The Palmaz-Schatz stent and a Wiktor stent were used in this particular example. Other stents have been used in other tests.

5. The stents were thoroughly cleaned using laboratory detergents and washed in warm water.

45 6. The stents were left to air dry in a sterile environment (sterile lamina flow hood).

7. The stents were then wetted with the solution by dipping them in the solution to the point where their entire surface was submerged in the liquid.

50

55

5

12

8. Using a specially designed lever, the stents were lifted out of the solution at
10 a rate of 1 mm/sec. This facilitated the uniformity of the coat.

9. The stents were left to air dry in a sterile environment (sterile lamina flow
15 hood) for 15 min.

10. Steps 7-9 were repeated 4 times in order to obtain the appropriate coating
15 thickness.

11. The stent was boiled in water for about 2 to 3 minutes.

12. After boiling, the stents were then air-dried at a slightly higher temperature.

13. The stents were then placed on an angioplasty balloon and were inflated to
20 85% of their range.

14. The stents were weighed and examined under a scanning microscope to
25 determine the uniformity of the coat and its attachment to the stent surface.

15. The stents' surface appeared to be completely covered and to a sufficient
25 level of uniformity. Coating adhesion remained intact even under severe stress.

It will be evident to those skilled in the art that the invention is not limited to the
30 details of the foregoing illustrative examples and that the present invention may be
embodied in other specific forms without departing from the essential attributes
thereof, and it is therefore desired that the present embodiments and examples be
35 considered in all respects as illustrative and not restrictive, reference being made to
the appended claims, rather than to the foregoing description, and all changes which
come within the meaning and range of equivalency of the claims are therefore
intended to be embraced therein.

40

45

50

55

Claims

5

10

15

20

25

30

35

40

45

50

55

5

13

WHAT IS CLAIMED IS:

10

1. A hemo-compatible, restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivative.

15

2. A hemo-compatible, restenosis-inhibiting metallic stent according to claim 1, comprising a coating of a poly-hydroxy methacrylate derivative selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethoxyethyl methacrylate) PMEEMA, poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof.

20

25

3. A process for producing hemo-compatible, restenosis inhibiting metallic stents comprising the steps of:

30

(a) coating a metallic stent with a liquid which contains a hydroxymethacrylate derivative selected from the group consisting of 2-hydroxyethyl-methacrylate; hydroxyethoxyethyl methacrylate, hydroxydiethoxyethyl methacrylate, methoxyethyl methacrylate, methoxyethoxyethyl methacrylate, methoxydiethoxyethyl methacrylate, ethylene glycol dimethacrylate and mixtures thereof;

35

(b) polymerization of said 2-hydroxy-methacrylate derivative into a polyhydroxymethacrylate derivative selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethoxyethyl methacrylate) PMEEMA, poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof; and

40

(c) cleaning the stent after polymerization to extract any remaining residues.

45

4. The process of claim 3 wherein the stent is cleaned in warm water.

50

55

5

14

10. 5. The process of claim 3 comprising the additional step of adding a cross linking agent.

15. 6. The process of claim 5, wherein said cross linking agent is present in an amount of about 0.1% to 6% weight relative to the weight of the 2-hydroxyethyl-methacrylate monomer.

20. 7. The process of claim 3 wherein the stent is first treated with a primer.

25. 8. The process of claim 3 wherein the stent is made from a metal in combination with a polymer.

30. 9. The process of claim 3 wherein the stent is made from stainless steel.

35. 10. The process of claim 3 wherein the stent is made from a Ti-based alloy.

40. 11. The process of claim 3 wherein the stent is made from a shape memory alloy.

45. 12. The process of claim 3 wherein the polymerization is carried out at atmospheric pressure.

50. 13. The process of claim 3 wherein the polymerization is carried out by dielectric heating.

14. The process of claim 3 wherein the polymerization is carried out by induction heating.

15. The process of claim 3 wherein the polymerization is initiated by at least one of photopolymerization, ionic-polymerization, and chemical-polymerization.

16. The process of claim 3 wherein the polymerization is carried out at elevated pressures.

17. The process of claim 3 wherein the polymerization is carried out at temperatures in the range of 150°C to 230°C.

18. The process of claim 5, wherein said cross linking agent is methacrylic diester of ethyleneglycol.

5

15

19. The process of claim 18, wherein said methacrylic diester of ethyleneglycol
10 is selected from the group consisting of:

- (a) tetraethyleneglycol dimetacrylate,
- (b) triethyleneglycol dimethacrylate,
- (c) diethyleneglycol dimethacrylate,
- 15 (d) monoethyleneglycol dimethacrylate, and
- (e) mixtures thereof.

20. The process of claim 3, wherein said poly-hydroxyethylmethacrylate
comprises a copolymer of monomeric 2-hydroxyethyl-methacrylate.

21. The process of claim 20, wherein said coating contains a cross linking
agent.

25. The process of claim 3 wherein NaOH is added before said polymerization
step.

30. The process of claim 22, wherein said at least 30% NaOH is used.

24. The process of claim 22, wherein said polymerization is effected at a
temperature of at least 90°C.

35. The process of claim 3, comprising diluting said
poly-hydroxyethylmethacrylate containing liquid in order to obtain different coating
thicknesses.

40. 26. A process for producing hemo-compatible bioactive restenosis inhibiting
metallic stents, comprising the steps of:

- a) coating a metallic stent with a liquid which contains
poly-hydroxyethylmethacrylate in liquid form;
- 45 b) cleaning the stent to extract any remaining toxic residues; and
- c) drying the same.

50

55

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 99/00376

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61L31/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2 226 129 A (HUELS CHEMISCHE WERKE AG) 3 July 1998 (1998-07-03) page 15, line 19 -page 16, line 14 page 20, line 23 -page 21, line 3 -----	1-12,15, 20,21,26
X	WO 96 25897 A (MENLO CARE INC) 29 August 1996 (1996-08-29) claims 1,4,6,14 -----	1-12,15, 20,21,26
A	EP 0 574 880 A (UNITED STATES SURGICAL CORP) 22 December 1993 (1993-12-22) page 4, line 46 - line 55 example 4 -----	1-3,5,6, 15, 18-21,26

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"A" document member of the same patent family

Date of the actual completion of the international search

26 October 1999

Date of mailing of the international search report

04/11/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentpoort 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 epo nl
Fax: (+31-70) 340-3016

Authorized officer

Heck, G

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IL 99/00376

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
CA 2226129 A	03-07-1998	DE	19723132 A	09-07-1998
		DE	19723131 A	09-07-1998
		EP	0852238 A	08-07-1998
		JP	10195390 A	28-07-1998
		NO	976154 A	06-07-1998
WO 9625897 A	29-08-1996	AU	4929696 A	11-09-1996
		CA	2213403 A	29-08-1996
		EP	0810845 A	10-12-1997
		US	5674241 A	07-10-1997
EP 0574880 A	22-12-1993	US	5366756 A	22-11-1994
		CA	2097244 A	16-12-1993
		US	5697976 A	16-12-1997



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: A61L 31/08, A61F 2/06, A61K 51/12, A61L 31/16, A61L 31/18	A1	(11) International Publication Number: (43) International Publication Date:	WO 00/12147 09 March 2000 (09.03.2000)
--	----	--	---

(21) International Application Number: (22) International Filing Date: (30) Priority Data: (60) Parent Application or Grant	PCT/US99/19697 31 August 1999 (31.08.1999) 09/145,707 02 September 1998 (02.09.1998) US SCIMED LIFE SYSTEMS, INC. [/]; () YANG, Dachuan [/]; () WANG, Lixiao [/]; () ANDERSON, William, E., II; ()	Published
--	---	-----------

(54) Title: DRUG DELIVERY DEVICE FOR STENT
(54) Titre: SYSTEME D'ADMINISTRATION DE MEDICAMENTS POUR STENT

(57) Abstract

A device adapted for mounting on a stent, the device comprising a sheath being made of polymeric material that includes drugs such as pharmaceutical agent(s) or radioactive agent(s) for delivery to an implant site. The sheath includes a main body of a generally tubular shape, and may include mounting means for attaching same to the stent. The device may have a slit therein, and may comprise a helical coil, a cylinder or any other suitable shape or design which fits a particular stent. The sheath may include a coating or coatings thereon containing drugs, surgical adhesives or a combination thereof.

(57) Abrégé

L'invention concerne un dispositif conçu pour être monté sur un stent. Ce dispositif comprend une gaine en matériau polymère contenant des médicaments, par exemple un ou plusieurs agent(s) pharmaceutiques, devant être administrés sur le site d'implantation. Cette gaine comprend un élément principal de forme sensiblement tubulaire et peut comprendre des moyens de fixation permettant de la fixer sur le stent. Le dispositif peut comprendre un fente ainsi qu'un enroulement hélicoïdal, un cylindre ou toute autre forme ou structure adaptée à un stent particulier. La gaine peut en outre comprendre une ou plusieurs couches de revêtement contenant des médicaments, des adhésifs chirurgicaux ou une combinaison des deux.

